Pediatric Focused Safety Review: ATACAND® (candesartan cilexitil) Pediatric Advisory Committee Meeting January 30, 2011

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Outline

- Background Information
- Pediatric Studies
- Pediatric Labeling Changes
- Additional Relevant Safety Labeling
- Drug Use Trends
- Adverse Events
- Summary

Background Drug Information

- **Drug: ATACAND® (candesartan cilexitil)**
- **Formulations:**
  - Non-scored tablets: 4, 8,16, and 32 mg
  - Oral suspension
- **Therapeutic Category**: Angiotensin II receptor blocker (ARB)
- Sponsor: Astra Zeneca

ATACAND® (Candesartan cilexitil) Market Approvals

Initial approval (June 4, 1998): Treatment of hypertension in adults (oral tablets)

February 22, 2005: Treatment of adults with heart failure NYHA class II-IV and ejection fraction ≤40% (oral tablets)

BPCA labeling change (October 22, 2009): Treatment of hypertension in children 1 to <17 years of age

ATACAND® (Candesartan cilexitil)- Dosing

	Starting Dose	Dose Range
Adult Hypertension	16 mg once daily	8 - 32 mg total daily dose
Pediatric Hypertension (1 to < 6 years)	0.20 mg/kg once daily	0.05 - 0.4 mg/kg once daily or consider divided dose
Pediatric Hypertension (6 to < 17 years)	< 50 kg 4 – 8 mg once daily > 50 kg 8 – 16 mg tablet once daily	< 50 kg 4 – 16 mg once daily or consider divided dose > 50 kg 4 – 32 mg once daily or consider divided dose

Note: Doses above 0.4 mg/kg have not been studied in patients 1 to < 6 years. Doses above 32 mg have not been studied in patients 6 to < 17 years.

Background Drug Information
ATACAND® (Candesartan cilexitil)

- Written Request (WR) issued Jan 30, 2007
- Three pediatric studies under BPCA (ages 1 to <17years):
  - Pharmacokinetic Study
  - Pediatric Safety and Efficacy Study
  - Pediatric One Year Safety Study
- Pediatric Exclusivity granted July 20, 2009
- BPCA labeling change October 22, 2009

ATACAND® (Candesartan cilexitil) Pediatric Studies Result- Pharmacokinetics

PK profile was comparable among children and adults and consistent across subgroups of age, weight and gender.

In children, Cmax/Cmin concentrations decline by over ten fold over a 24-hr interval.

PK (Cmax and AUC) were not modified by age, sex or body weight.

ATACAND® (Candesartan cilexitil) Pediatric Study Results: Efficacy study 1

Randomized, DB, multicenter, dose-ranging study in 93 children.

Ages: 1 to 6 years with hypertension, 74% with renal disease.

Primary endpoint: Change in systolic blood pressure (SBP) .

Result: SBP and DBP decreased 6.0/5.2 to 12.0/11.1 mmHg from baseline across 3 doses (0.05, 0.20 or 0.40mg/kg/day).

ATACAND® (Candesartan cilexitil) Pediatric Study Results- Efficacy study 2

Randomized, DB, PC, multicenter study conducted in 240 children aged 6 to <17 years.

Primary endpoint: Change in systolic blood pressure (SBP).

Results: significant decrease in systolic/diastolic blood pressure ranged from 4.9/3.0 to 7.5/7.2 mmHg.

ATACAND® (candesartan celexitil)
Relevant safety labeling
Boxed Warning

Warning: USE IN PREGNANCY:
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, ATACAND should be discontinued as soon as possible

ATACAND® (candesartan celexitil) Safety labeling

4. Contraindications: ATACAND is contraindicated in patients who are hypersensitive to any component of this product.

5. Warning and Precautions-

5.1 Fetal and neonatal morbidity and mortality can result when drugs that act directly on the renin-angiotensin system (RAS) are administered to pregnant women. When pregnancy is detected ATACAND should be discontinued as soon as possible.

5.2 Morbidity in Infants: Children < 1 year of age must not receive ATACAND for hypertension. ATACAND and drugs that act directly on the RAS can have negative consequences on the development of immature kidneys. ATACAND has been shown to cause abnormal kidney development in very young mice.

ATACAND® (candesartan celexitil) Warning and Precautions- Continued

5.3 Hypotension: In adults or children with volume and/or salt depletion, for example those being treated with diuretics, symptomatic hypotension may occur. These conditions should be corrected prior to administration of ATACAND or the treatment should start under close medical supervision.

5.4 Impaired Hepatic Function: Significant increases in candesartan AUC and Cmax can occur. A lower initiating dose of ATACAND should be considered for patients with moderate hepatic impairment.

5.5 Renal Function Deterioration: ATACAND has not been studied in children with estimated glomerular filtration rate < 30 mL/min/1.73 m2.

ATACAND® (candesartan celexitil)

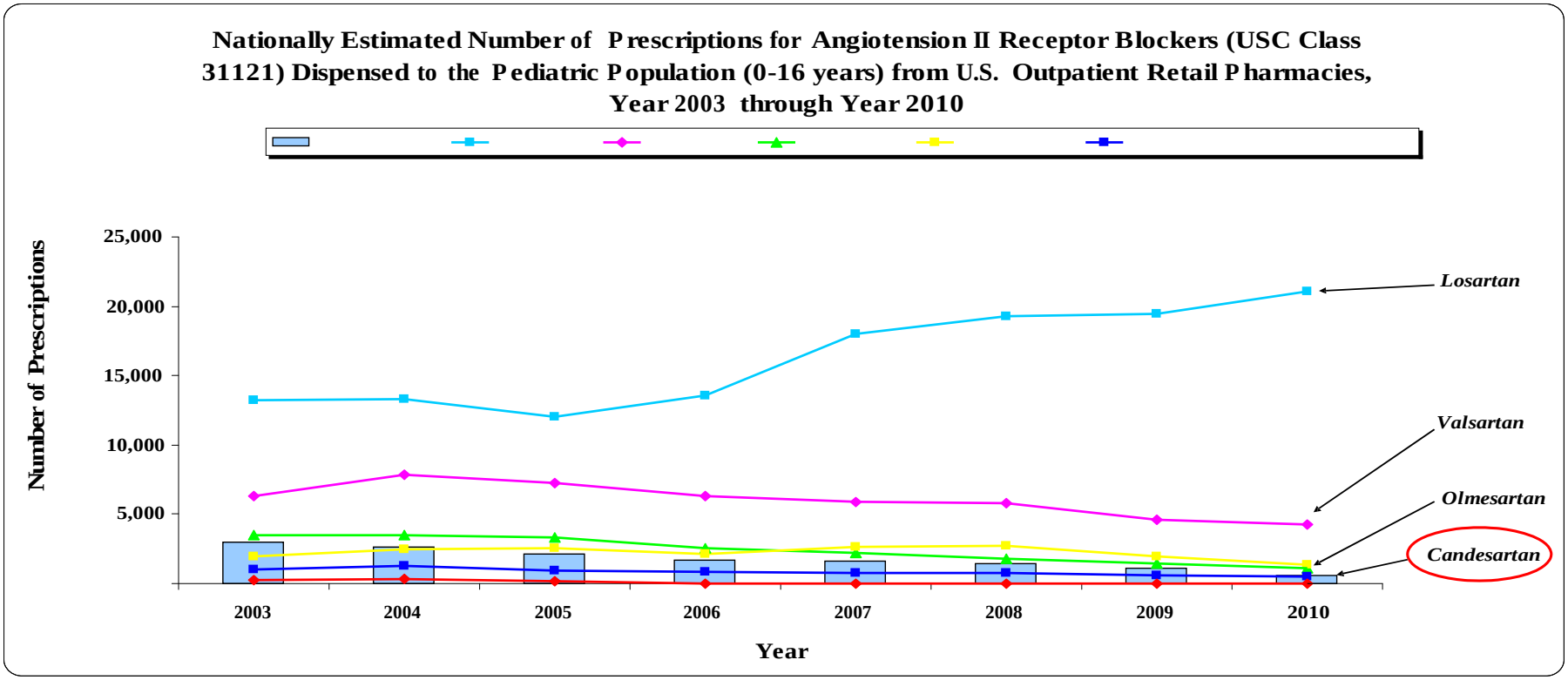
6. ADVERSE REACTIONS

6.1 Clinical Studies Experience

1 in 93 children aged 1 to < 6 years and 3 in 240 children aged 6 to < 17 years experienced worsening renal disease. The association between candesartan and exacerbation of the underlying condition could not be excluded.

Atacand® (candesartan) Drug Utilization

Top ARB Prescriptions Dispensed to the Pediatric Population U.S. Outpatient Retail Pharmacy Setting[1]



- Losartan was the most commonly dispensed medication among the patients aged 0-16 years
- During year 2010, candesartan was the fifth most frequently dispensed medication

[1]IMS, Vector One®: National VONA. Year 2003 to Year 2010. Data Extracted November 2011.

Atacand® (candesartan) Drug Utilization U.S. Outpatient Retail Pharmacy Setting April 2002 – July 2011, cumulative1

- **Total population:** 20.1 million prescriptions and 1.7 million patients were dispensed prescriptions for candesartan
- **Pediatric population:** 17,000 prescriptions and 3,700 patients aged 0 to 16 years received candesartan (accounted for less than 1% of total use)
  - 63% of pediatric patients aged 6-16 years
  - 37% of pediatric patients aged 1-5 years
  - 5% of pediatric patients aged < 1 year

Atacand® (candesartan) Drug Utilization

Prescribing Specialty and Diagnosis

April 2002 – July 2011, cumulative[1]

- Top prescribing specialties for candesartan prescriptions were Internal Medicine and General Practice/Family Medicine
- Pediatricians accounted for less than 1% of candesartan prescriptions
- Only diagnosis captured in pediatric patients aged 0-16 years was “Hypertension” (ICD-9 code 401.9)

Total Number [1] of ATACAND® (candesartan) Adverse Events Reports April 1, 2002 to July 31, 2011

	All reports (US)[2]	Serious (US)[3]	Death (US)
Adult (≥ 17 yrs.)	3463 (592)	3007 (276)	246 (27)
Pediatric (0-16 yrs.)	**69 (7)[4]**	66 (5)	19 [5] (1)
Age unknown (null values)	574 (314)	318 (74)	44 (8)[4]
Total	4106 (913)	3391 (355)	309 (36)

[1] May include duplicates

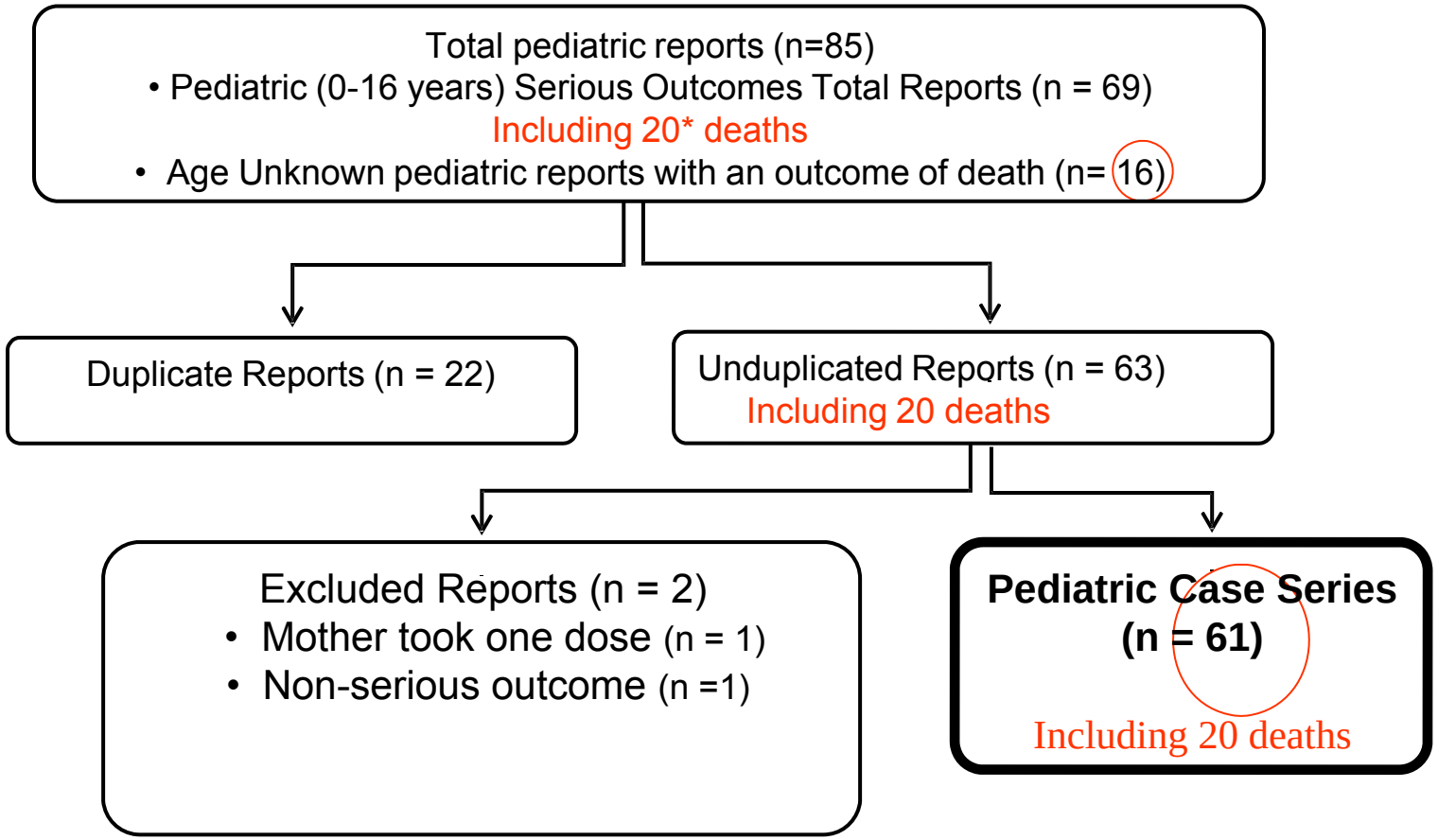
[2] US counts in parentheses

[3] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

[4] See next slide

[5] Includes one additional fatal case that was miscoded with an outcome of hospitalization

Selection of Pediatric AERS cases with serious outcome ATACAND® (candesartan celexitil) (April 1, 2002 to July 31, 2011)

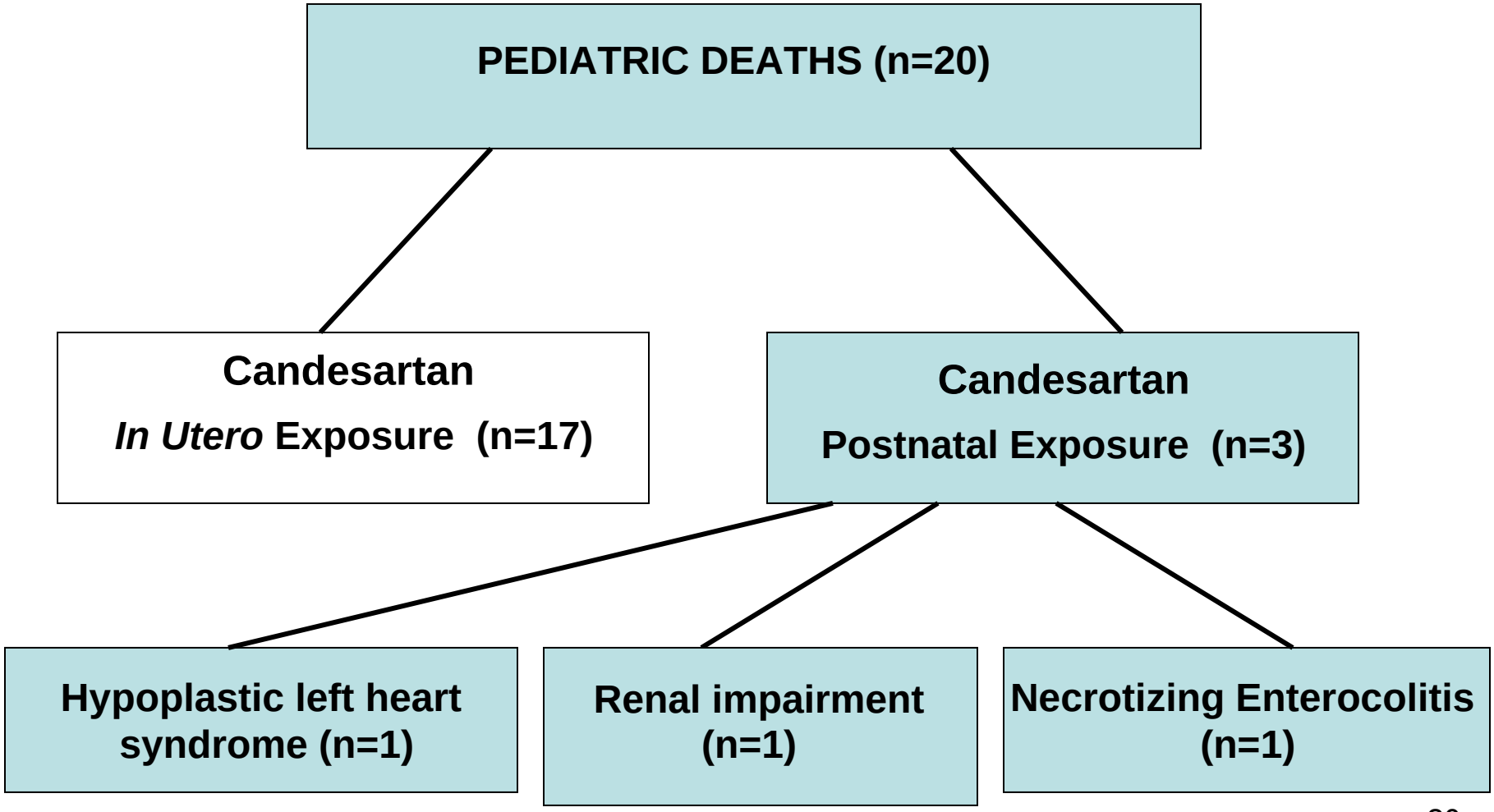


ATACAND® (candesartan celexitil) Adverse Events Reports

The majority of pediatric deaths and serious adverse events were related to

in utero candesartan exposure.

Pediatric Deaths



Pediatric Deaths Associated with Post Natal Candesartan Exposure- Continued

Hypoplastic left heart syndrome a newborn female baby with hypoplastic left heart syndrome, heart failure and decreased urine output who received candesartan 0.15 mg/day. Two days after the initiation of candesartan, her urine output decreased and her edema was aggravated. The patient was put on IV furosemide and candesartan dose was increased to 0.3 mg/day. The increase was not tolerated, thus, candesartan dose was lowered to 0.15 mg/day, after which she improved. At 8 months of age, the patient underwent cardiac surgery, and later developed cardiac failure and died. Autopsy showed thinning and fibrosis of the inferior wall of the right ventricle.

Pediatric Deaths Associated with Post Natal Candesartan Exposure

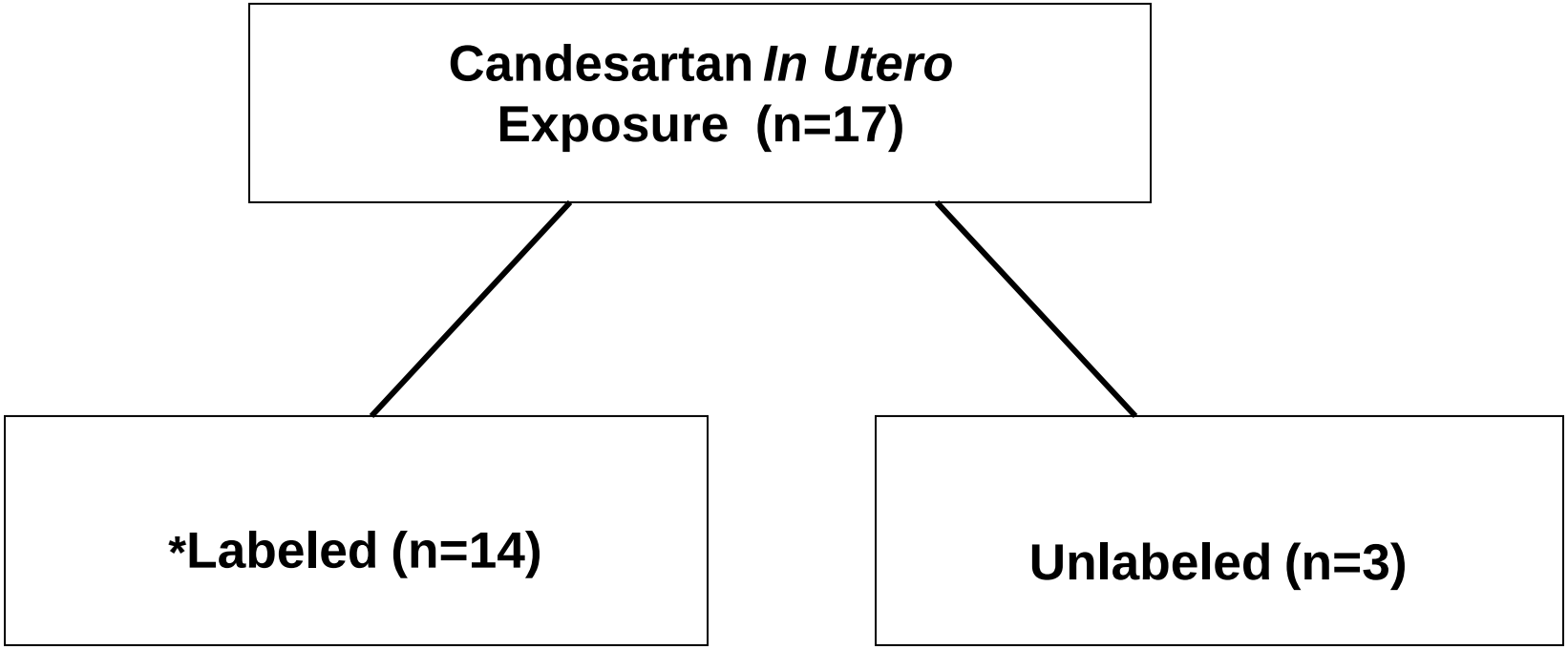
Renal impairment a 3 year-old child with nephrotic syndrome and focal segmental glomerulonephritis was enrolled in a candesartan study and was on concomitant drugs. The child had recurrent viral infections since birth and later developed coagulopathy and died. Autopsy showed chronic bilateral renal disease, lung edema, and anasarca.

Pediatric Deaths Associated with Post Natal Candesartan Exposure- Continued

Necrotizing enterocolitis a one year-old with a H/O multiple cardiac surgeries since the age of 6 days was started on candesartan 0.3 mg/day at the age of eight months. The patient was on furosemide, spironolactone, warfarin, propranolol, and acetylsalicylic acid. Ten months after candesartan treatment, the patient developed necrotizing enterocolitis (NEC) and subsequently died. Autopsy was performed but results were unknown.

Necrotizing enterocolitis (NEC) developed 10 months after the initiation of candesartan treatment. The occurrence of NEC is more common in newborns with congenital heart defect, due to the associated disturbance in circulation.

In Utero Deaths Associated with Candesartan Exposure



Events characteristic of a drug that acts on RAS

In Utero Deaths with Events* (n=14)

- Oligohydramnios (n=7)
- Renal failure, impairment or anuria (n=6)
- Pulmonary hypoplasia (n=5)
- Skull malformation (n=5)
- Prematurity (n=5)
- Hypotension (n=2)
- Potter's syndrome (n=2)
- Bladder agenesis (n=1)
- Limb contracture (n=1)
- Congenital heart defects (n=1)
- Umbilical cord abnormality (n=1)
- Fetal disorder (n=1) (Unstated)

**Some cases reported one or multiple event(s)*

Underlined events are unlabelled

Non-Fatal Serious Pediatric Adverse events Associated with Candesartan Exposure (n=41)

Post natal exposure (n=16)

- **Labeled events (n=3)**
- **Unlabeled events (n=13)**

In utero exposure (n=25)

Post Natal Candesartan Exposure Labeled Events* (n=3)

Labeled events:

- **Renal failure (n=1)**
- **Hypotension (n=1)**
- **Pruritus (n=1)**

**Overall these 3 cases were either confounded by underlying diseases or lacked clinical information for assessment*

Post Natal Candesartan Exposure Unlabeled Events* (n=13)

Unlabeled events

- **Accidental ingestion (n=5)**
- **Intentional overdose (n=2)**
- **Secondary renal failure (n=1)**
- **Convulsion (n=2)**
- **Medication error (n=1)**
- **Lymphedema (n=1)**
- **Growth hormone deficiency (n=1)**

**Overall these 13 cases were either confounded by underlying diseases or lacked clinical information for assessment*

Post Natal Candesartan Exposure

Summary of cases with labeled events with

Hypotension (n=1), an 11 year-old female patient with a history of adrenal cortical insufficiency presented with paleness, fatigue, and hypotension after receiving one dose of candesartan 16 mg. The patient was on HCTZ and isradipine for hypertension. The patient improved after candesartan and isradipine were discontinued. *Candesartan is labeled for hypotension. H/O concomitant use of hydrochlorothiazide and isradipine.*

Pruritus (n=1), a 14 year-old female patient experienced hypertrichosis and generalized pruritus following candesartan administration. Candesartan was discontinued and pruritus resolved after switching the patient to valsartan. Candesartan challenge test was negative. *Candesartan is labeled for pruritus.*

Renal failure (n=1), a 14 year-old male was hospitalized with the diagnoses of congenital abdominal aortic stenosis, renal hypertension, and ruptured cerebral aneurysm. The patient developed oliguria after the initiation of candesartan, and was put on hemodialysis and subsequently improved. *(Candesartan inhibits the RA-aldosterone system, therefore, changes in renal function may be anticipated).*

Cases with Post Natal Candesartan Exposure- Continued

Convulsions (n=3)

3 year-old male patient with a H/O total cavopulmonary connection for single ventricle and intracranial hemorrhage. The patient was on warfarin, aspirin, and candesartan. Eight months after starting candesartan, the patient developed convulsions. EEG showed central sharp waves. The patient was diagnosed with epilepsy post intracranial hemorrhage and was started on sodium valproate. No additional convulsions were reported. *It is possible that the epilepsy was due to underlying intracranial hemorrhage in this case*.

A 2 month-old baby who was breast-fed, developed seizures while the mother was taking candesartan for hypertension. Candesartan was discontinued. No information on the outcome of the baby's condition.

A 31 week old female baby who presented with intracranial hemorrhage (ICH), skull fracture, hyponatremia and convulsions, (the patient may have been given candesartan by a parent) possibly as a result of child abuse. The patient was hospitalized, but no report on outcome. *Convulsions likely related to ICH and skull fracture.*

Summary of Cases with Post Natal Candesartan Exposure- Continued

Accidental ingestion (n=5), all were reported in females; ages ranged from 1 to 3 years in four cases and one report was in an infant of unspecified age.

Intentional overdose (n=2), a 13 year-old male with a history of unspecified mental illness, was suspected to have ingested multiple candesartan and amlodipine tablets. He responded to diuretic and vasopressor treatment. A 13 year-old female took her father's prescription of rosuvastatin and candesartan in a suicide attempt. She hospitalized and improved.

Medication error (n=1), a 10 year-old male with a H/O chronic kidney disease. The patient was on methylphenidate, cyproheptadine, tolterodine (detrol), loratadine, enalapril, and desmopressin. Two days after mistakenly taking AVANDIA (rosiglitazone) instead of ATACAND, the patient experienced irritability, visual difficulty, hunger, and profuse sweating. Avandia was discontinued.

Cases with Post Natal Candesartan Exposure- Continued

Growth hormone deficiency (n=1), a 12 year-old male with coarctation of the aorta and hypertension, who developed growth hormone deficiency after starting doxazosin, amlodipine, candesartan and amitriptyline. Growth hormone deficiency resolved without treatment 2 years after discontinuation of the anti-hypertensives. *There is no clear association to a clinical diagnosis of growth hormone deficiency.*

In Utero Non-Fatal Adverse Events (n=25)

18 cases reported labeled* events and 7 case reported unlabeled events

- Renal failure/renal impairment/anuria (n=14)
- Hypotension (n=6)
- Oligohydramnios (n=5)
- Skull malformation (n=5)
- Pulmonary hypoplasia (n=3)
- Clubfoot (n=1)

Overall, these cases lacked information, such as mother's medical history or concomitant drugs and therefore, drug-event relationship is difficult to assess.

**Adverse events characteristic of drugs that act on the RAS.*

In Utero Unlabeled Adverse Events (n= 7)

- Acute respiratory distress syndrome (n-2)
- Renal vein thrombosis (n=1)
- Neonatal asphyxia (n=3)
- Neonatal Jaundice (n=1)
- Hypospadias (n=1)
- Osteogenesis imperfecta (n=3)
- Cyanosis and Hypotonia (n=3)

Summary Pediatric Focused Safety Review ATACAND® (candesartan celexitil)

- This concludes ATACAND pediatric focused safety review.
- Labeling has been changed to grant an indication for pediatric hypertension in children 1 year and older.
- No new safety signals were identified
- The FDA recommends continued routine monitoring. Does the Committee concur?

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